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. PaO_2, $PaCO_2$, 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 [± 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 $PaCO_2$ 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: D_{LCO} = 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; $\dot{V}e_{MAX}$ = 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 function.[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 recoil[12] 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 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 (Sa_{O_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 postbronchodilator values (except DLCO) and are reported in absolute numbers or as a percentage of normal predicted.[31–33] The craniocaudal 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 Sa_{O_2}, minute ventilation ($\dot{V}E$), tidal volume (VT), 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 Sa_{O_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 ≤ 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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†A list of centers and participants in the National Emphysema Treatment Trial Research Group is located in the Appendix.
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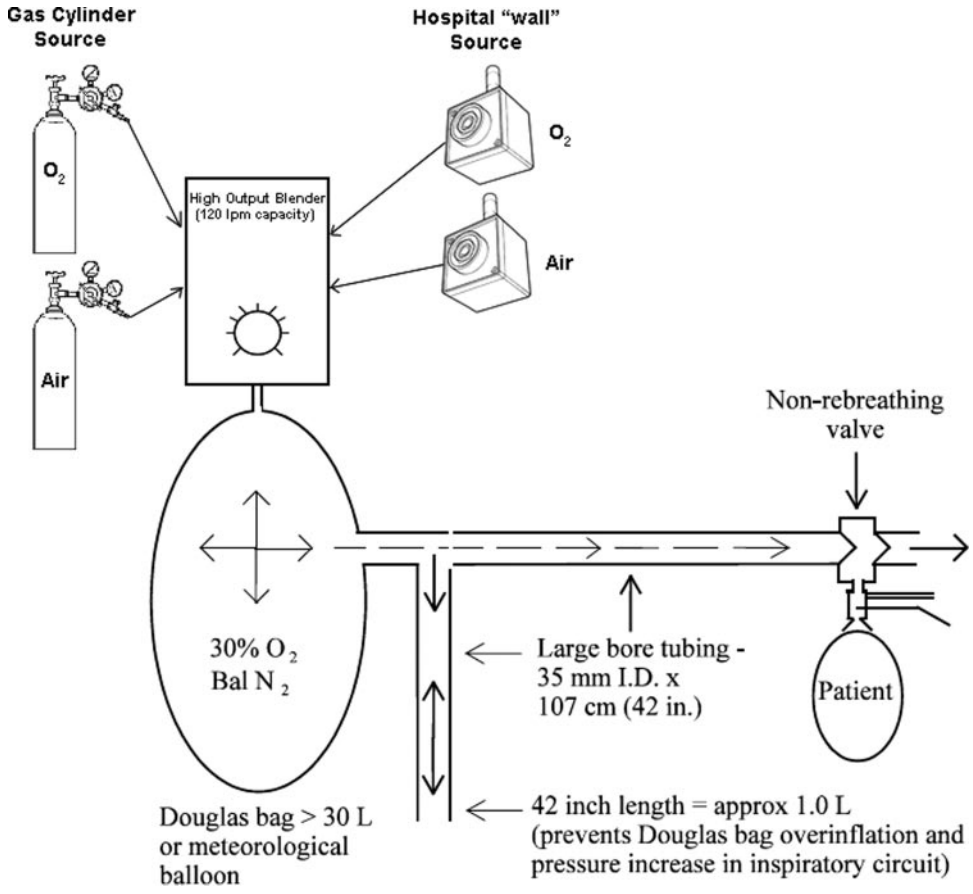

FIGURE 1. Schematic showing delivery of high-flow 30% inspired oxygen to avoid fluctuations in inspired oxygen concentration at all levels of ventilation encountered during exercise.

exercise values included maximum watts on the cycle recorded when workload was terminated or cadence dropped below 40 rpm and did not return. All maximum data were recorded from the same 20-s interval. Borg Scale ratings were recorded at maximum exertion. Expired gas measurements were reported from the last 20-s interval of collection before test termination.

Dead Space Calculation

The dead space fraction was calculated using the Enghoff modification of the Borg equation.[36] Arterial blood gas determinations and expired carbon dioxide concentrations were obtained at identical time points.

Definitions of Exercise Limitation

Ventilatory limitation was defined as either the presence of a maximum $\dot{V}E$ ($\dot{V}E$max)/maximal ventilatory volume (MVV) ratio $\geq$ 85, or MVV $-$ $\dot{V}E$max $<$ 8 L. Cardiovascular limitation was defined as 100 $\times$ heart rate/(220 $-$ age) $\geq$ 90 for men, and as 100 $\times$ heart rate/(226 $-$ age) $\geq$ 90 for women. Patients were then classified as to the presence or absence of ventilatory or cardiac limitations to perform maximum exercise.

Statistical Analysis

Patients who could pedal with the cycle ergometer set at 0 W only were considered to have a maximum workload of 0 W, and values measured at unloaded pedaling were considered to be measures at maximum effort. Mean values for continuous variables were compared using two-sample t tests; distributions of categorical variables were compared using χ^2 tests. Differences between the two treatment groups in the relationship between paired continuous measures from the three sampling times (after 5 min of rest on the mouthpiece, after 3 min of unloaded pedaling, and at maximum effort) were assessed for each follow-up time using generalized estimating equations with robust variance estimation[37] to account for the correlation between observations from the same patient. The linear model included the dependent continuous measure as the outcome and terms for treatment group, sampling phase (rest, unloaded, or maximum), and the interactions between these two variables; the p value was derived under the assumption that the treatment and treatment times phase interaction terms were equal to zero. Analyses were limited to patients completing testing at each time point included in the analysis so a patient who missed an assessment was excluded.

RESULTS

Baseline Patient Demographics and Lung Function

In comparison to the total population, patients enrolled in the exercise substudy were more likely to be men, were slightly more hypoxemic at rest, with lower

Table 1—*Baseline Demographics, Respiratory Function, and Emphysema Distribution

Characteristics	All Patients		Substudy Patients	
	LVRS (n = 608)	Medical (n = 610)	LVRS (n = 116)	Medical (n = 122)
Age at randomization, yr	66.5 ± 6.3	66.7 ± 5.9	66.2 ± 7.2	66.0 ± 6.4
Male gender, %	58.4	64.1	62.1	71.3
BMI, kg/m^2	24.5 ± 3.7	24.7 ± 3.5	24.4 ± 3.7	24.7 ± 3.6
Pa_{O_2}, mm Hg	64.5 ± 10.5	64.2 ± 10.1	62.9 ± 11.8	62.6 ± 10.2
Pa_{CO_2}, mm Hg	43.3 ± 5.9	43.0 ± 5.8	41.8 ± 5.2	42.4 ± 5.7
PH	7.42 ± 0.03	7.42 ± 0.03	7.43 ± 0.03	7.42 ± 0.03
FEV_1, L	0.76 ± 0.24	0.78 ± 0.24	0.76 ± 0.24	0.80 ± 0.26
FEV_1, % predicted	26.8 ± 7.4	26.7 ± 7.0	26.7 ± 7.6	27.1 ± 7.1
RV, % predicted	220.5 ± 49.9	223.3 ± 48.9	218.3 ± 52.2	219.8 ± 49.2
TLC, % predicted	128.0 ± 15.3	128.5 ± 15.0	128.3 ± 15.1	127.7 ± 14.2
DLCO, % predicted	28.3 ± 9.7	28.4 ± 9.7	27.7 ± 10.3	29.1 ± 8.9
Hgb, g/dL	14.4 ± 1.3	14.3 ± 1.3	14.4 ± 1.5	14.2 ± 1.3
Emphysema location,† %				
Upper lobe	67.7 ± 21.9	69.9 ± 20.8	69.1 ± 23.1	67.7 ± 22.4
Lower lobe	49.8 ± 18.4	51.5 ± 17.8	54.1 ± 18.4	52.3 ± 19.0
Total	55.8 ± 15.9	57.6 ± 15.3	59.1 ± 15.8	57.4 ± 16.8
Upper lobe-predominant,‡ %	63.3	66.5	62.1	55.4

*Values are given as the mean ± SD, unless otherwise indicated. BMI = body mass index; Hgb = hemoglobin; pH = arterial pH; RV = residual volume; TLC = total lung capacity.

†Determined from radiologist scores (0 to 4) for the percentage of emphysema seen on chest CT scans, in each of the upper, middle, and lower zones of each lung. The upper lobe percentage is the mean of the midpoints of the ranges represented by the right and left upper lobe scores. The lower-lobe percentage is the mean of the midpoints of the ranges represented by the right and left middle and lower lobe scores. The total percentage is the mean of the midpoints of the ranges represented by the upper, middle, and lower lobe scores of both lungs.

‡Determined from the radiologist's assessment of the craniocaudal distribution of emphysema seen on chest CT scans. The choices were 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.

Pa_{O_2} and lower Pa_{CO_2} values, and were less likely to have upper-lobe-predominant emphysema (Table 1).

Maximum Exercise Outcomes at Baseline and LVRS Effects Postrandomization

At baseline, the medical group achieved higher $\dot{V}_E$ and workload during maximum exercise than those randomized to LVRS ($p < 0.05$ for both measures; Table 2). Six months after randomization the LVRS patients achieved higher $\dot{V}_E$, $\dot{V}_{CO_2}$, V_T, heart rate, and workload ($p < 0.05$ for each measure), and lower Borg score for dyspnea ($p = 0.0001$) during maximum exercise than those patients assigned to medical therapy. LVRS and medical patients had similar systolic BP, diastolic BP, respiratory rate, and Borg score for leg fatigue.

Table 2—*Measurements During Maximum Exercise at Baseline and 6, 12, and 24 Months Postrandomization to Treatment, for Patients Completing Testing at All Time Points

Characteristics	Baseline			6 mo			12 mo			24 mo		
	LVRS (n = 287)	Medical (n = 216)	p Value	LVRS (n = 287)	Medical (n = 216)	p Value	LVRS (n = 287)	Medical (n = 216)	p Value	LVRS (N = 287)	Medical (n = 216)	p Value
$\dot{V}_E$, L/min	28.3	30.2	0.03	32.8	29.6	0.001	31.5	29.1	0.01	29.7	27.7	0.03
$\dot{V}_{CO_2}$, L/m	0.804	0.852	0.07	0.923	0.820	0.0003	0.890	0.807	0.005	0.831	0.759	0.01
V_T, L	1.01	1.06	0.08	1.18	1.07	0.001	1.15	1.05	0.002	1.09	1.01	0.03
HR, beats/min	121.5	121.0	0.75	124.4	120.7	0.02	123.9	120.7	0.03	121.6	118.8	0.06
RR, breaths/min	29.0	29.2	0.69	28.4	28.6	0.74	28.1	28.8	0.24	28.1	28.3	0.73
SBP, mm Hg	189.7	189.8	0.97	187.2	184.5	0.31	188.1	184.6	0.21	185.5	183.9	0.54
DBP, mm Hg	94.2	93.0	0.26	91.1	92.6	0.21	91.0	92.2	0.28	90.4	90.9	0.68
Borg score for dyspnea	5.0	5.0	0.97	4.4	5.2	0.0001	4.6	5.4	< 0.0001	4.9	5.3	0.05
Borg score for muscle fatigue	4.1	4.4	0.20	4.5	4.7	0.31	4.5	4.7	0.46	4.6	4.8	0.31
Load, W	42.1	48.1	0.01	49.3	45.1	0.04	49.0	43.3	0.01	44.9	40.7	0.05

*The number of individual measures ranged from 277 to 287 for the LVRS group, and from 205 to 216 for the medical group. DBP = diastolic BP; HR = heart rate; RR = respiratory rate; SBP = systolic BP.

Table 3—*Ventilatory and Cardiovascular Limitation During Maximum Exercise at Baseline and 6, 12, and 24 Months Postrandomization to Treatment, by Chest CT Scan Pattern of Emphysema, for Patients with Measures at All Time Points

	Baseline			6 mo			12 mo			24 mo		
Type of Limitation	LVRS, %	Medical, %	p Value	LVRS, %	Medical, %	p Value	LVRS, %	Medical, %	p Value	LVRS, %	Medical, %	p Value
All patients												
Ventilatory and cardiovascular	11.2	12.1		8.3	9.6		11.9	8.5		10.5	12.1	
Ventilatory only	67.9	62.3		49.5	71.9		54.2	67.8		60.3	64.8	
Cardiovascular only	2.2	1.5		7.9	3.0		6.5	3.5		5.4	1.0	
Neither	18.8	24.1		34.3	15.6		27.4	20.1		23.8	22.1	
Total	100	100	0.48	100	100	0.001	100	100	0.03	100	100	0.07
Patients, No.	277	199		277	199		277	199		277	199	
MVV, L/min BTPS												
Mean	32.0	34.5	0.01	40.4	33.9	< 0.001	38.0	33.7	0.001	35.1	33.1	0.12
SD	10.2	11.2		14.1	11.5		13.6	12.8		13.0	13.9	
Patients with upper lobe-predominant emphysema												
Ventilatory and cardiovascular	12.0	10.4		6.8	8.8		11.5	8.8		10.5	13.6	
Ventilatory only	67.0	67.2		48.2	73.6		50.8	69.6		57.1	65.6	
Cardiovascular only	1.6	0.8		7.9	2.4		8.4	1.6		7.9	0.8	
Neither	19.4	21.6		37.2	15.2		29.3	20.0		24.6	20.0	
Total	100	100	0.87	100	100	0.001	100	100	0.03	100	100	0.02
Patients, No.	191	125		191	125		191	125		191	125	
MVV, L/min BTPS												
Mean	31.8	34.0	0.08	41.4	33.6	< 0.001	39.2	33.6	0.001	36.5	33.3	0.06
SD	10.2	11.3		14.8	12.1		14.2	13.6		13.6	15.3	
Patients with non—upper-lobe-predominant emphysema												
Ventilatory and cardiovascular	9.3	14.9		11.6	10.8		12.7	8.1		10.5	9.5	
Ventilatory only	69.8	54.1		52.3	68.9		61.6	64.9		67.4	63.5	
Cardiovascular only	3.5	2.7		8.1	4.1		2.3	6.8		0	1.4	
Neither	17.4	28.4		27.9	16.2		23.3	20.3		22.1	25.7	
Total	100	100	0.19	100	100	0.15	100	100	0.42	100	100	0.68
Patients, No.	86	74		86	74		86	74		86	74	
MVV, L/min BTPS												
Mean	32.4	35.3	0.09	38.2	34.4	0.03	35.4	34.0	0.44	31.8	32.7	0.61
SD	10.2	11.2		12.0	10.5		11.9	11.6		11.0	11.3	

*One patient in the medical group did not have a chest CT scan for classification of the pattern of emphysema. The p value for LVRS and medical groups in the distribution of the type of limitation was determined by χ^2 test. The p values for the LVRS and medical groups in mean MVV was determined by *t* test. BTPS = body temperature and pressure saturated.

Effect of LVRS on Cardiac or Ventilatory Limitations to Perform Maximum Exercise

At baseline, approximately two thirds of patients randomized to the LVRS and medical groups manifested only ventilatory limitation during exercise (Table 3). Approximately 11 to 12% of patients had both ventilatory and cardiac limitation; few patients had only cardiac limitation. Distributions in the treatment groups were similar (p = 0.48). Six months after randomization, the distributions in the treatment groups were different (p = 0.001). In the LVRS group, there was a marked reduction in the percentage of patients who developed ventilatory limitation only. In contrast, the percentage of medical group patients with only ventilatory limitation had increased. These patterns of change were observed in patients with both upper-lobe and non–upper-lobe-predominant emphysema.

Effects of LVRS on Gas Exchange at Rest and During Maximum Exercise in Substudy Patients

The relationship of Pa_{CO_2} to $\dot{V}_{CO_2}$ at rest, during unloaded cycling, and during maximum exercise is shown in Figure 2 for patients with measurements made at baseline and at 6, 12, and 24 months after randomization, by emphysema distribution. At baseline, regardless of emphysema distribution, patients were eucapnic at rest, and they developed mild hypercapnia during unloaded cycling, with sharp and steep increases in Pa_{CO_2} during maximum exercise. Patients with upper-lobe-predominant emphysema randomized to LVRS had a downward shift in the relationship of Pa_{CO_2} vs $\dot{V}_{CO_2}$ at rest,

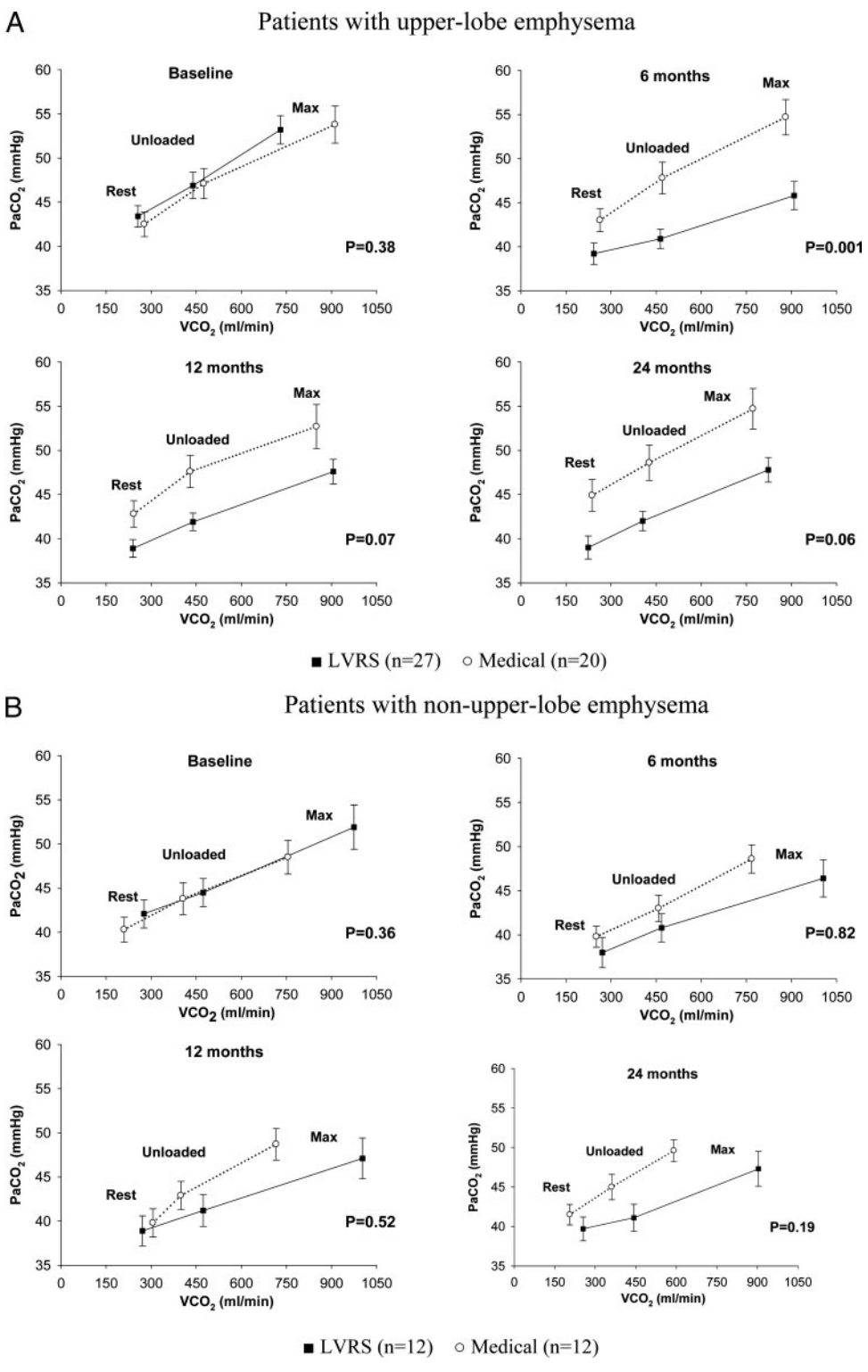

FIGURE 2. Impact of upper-lobe vs non-upper-lobe emphysema on the relationship of $PaCO_2$ to $\dot{V}CO_2$ during restful breathing, unloaded cycling, and maximum exercise at baseline and 6, 12, and 24 months postrandomization to treatment, for substudy patients completing testing at all time points. Error bars show the $PaCO_2$ SEM in each phase of testing.

Table 4—*Pao_2 During Restful Breathing, Unloaded Pedaling, and Maximum Exercise at Baseline and at 6, 12, and 24 Months Postrandomization to Treatment, for Patients Completing Testing at All Time Points

	Baseline			6 mo			12 mo			24 mo		
Variables	LVRS (n = 39)	Medical (n = 32)	p Value	LVRS (n = 39)	Medical (n = 32)	p Value	LVRS (n = 39)	Medical (n = 32)	p Value	LVRS (n = 39)	Medical (n = 32)	p Value
Resting	107.2	106.9	0.96	117.0	110.2	0.24	121.6	110.4	0.06	122.4	110.7	0.08
Unloaded	97.6	101.6	0.49	107.8	103.9	0.51	112.0	104.6	0.25	113.0	102.3	0.10
Maximum	88.3	98.7	0.10	93.7	97.7	0.52	94.4	98.6	0.54	93.8	93.9	0.99

*Patients inspired 30% or 31% oxygen during testing.

during unloaded cycling, and during maximum exercise that was evident at 6 months ($p = 0.001$), and was borderline significant at 12 months ($p = 0.07$) and 24 months ($p = 0.06$) compared to medical patients. These differences between treatment groups were not seen during follow-up in the non–upper-lobe-predominant group.

Table 4 shows Pao_2 at rest, during unloaded cycling, and at maximum exercise at baseline and 6, 12, and 24 months after randomization for patients tested at all four testing times. There was no difference between treatment groups in level of oxygenation during unloaded pedaling, and maximum exercise at any of the follow-up times.

Effects of LVRS on Breathing Pattern at Rest and During Exercise

At baseline, LVRS and medical group patients with upper-lobe-predominant emphysema generated similar Vt during unloaded pedaling and at maximum exercise (Fig 3). Six, 12, and 24 months after randomization, LVRS patients with upper-lobe-predominant emphysema generated higher Vt values during unloaded cycling and maximum exercise than similar medical group patients ($p < 0.01$ for each time point). LVRS and medical group patients with non–upper-lobe-predominant emphysema had similar Vt generation during unloaded pedaling and at maximum exercise at each time point.

Figure 4 shows the effect of LVRS vs medical therapy on rapid shallow breathing during maximum exercise. Following LVRS, patients breathed deeper and slower at 6 months ($p = 0.01$) and 12 months ($p = 0.006$).

Effects of LVRS on Ventilatory Dead Space During Maximum Exercise

LVRS and medical patients had similar ventilatory dead space levels at baseline ($p = 0.21$), but LVRS patients had significantly lower levels than medical patients at 6 months ($p = 0.007$) and 24 months ($p = 0.006$) [Fig 5, *left*, *A*]. When ventilatory dead space was measured at an iso-workload time point (ie, unloaded pedaling) [Fig 5, *right*, *B*], LVRS and medical patients had similar ventilatory dead space levels at baseline ($p = 0.58$), but LVRS patients had significantly lower levels than medical patients at 6 months ($p = 0.005$), 12 months ($p = 0.02$), and 24 months ($p = 0.002$).

Effects of LVRS on Dyspnea at Rest and During Maximum Exercise

At 12 months after randomization, regardless of the CT scan pattern of emphysema, LVRS patients had a significant reduction in breathlessness during unloaded cycling and maximum exercise compared to medical patients (Fig 6).

Discussion

We previously reported that exercise capacity improved by > 10 W in 15% of LVRS patients compared with 3% of the medical therapy patients ($p < 0.01$).[26] Our present study extends these findings by showing that improved exercise following LVRS is due to the following improvements in ventilatory mechanics: less rapid and shallow breathing, reductions in ventilatory dead space, and enhanced carbon dioxide elimination. Approximately two thirds of our patients had ventilatory limitation as the primary etiology of early exercise termination. Approximately 11 to 12% had ventilatory and cardiac limitation, and rare patients had cardiac limitation alone. LVRS resulted in an approximately 20% reduction in the percentage of patients exhibiting ventilatory limitation as a primary cause for exercise termination. These data support improvements in lung,[14,15,18,26,27] chest wall,[9,16] and respiratory muscle mechanics,[5,7] as responsible for enhancing exercise performance following LVRS.

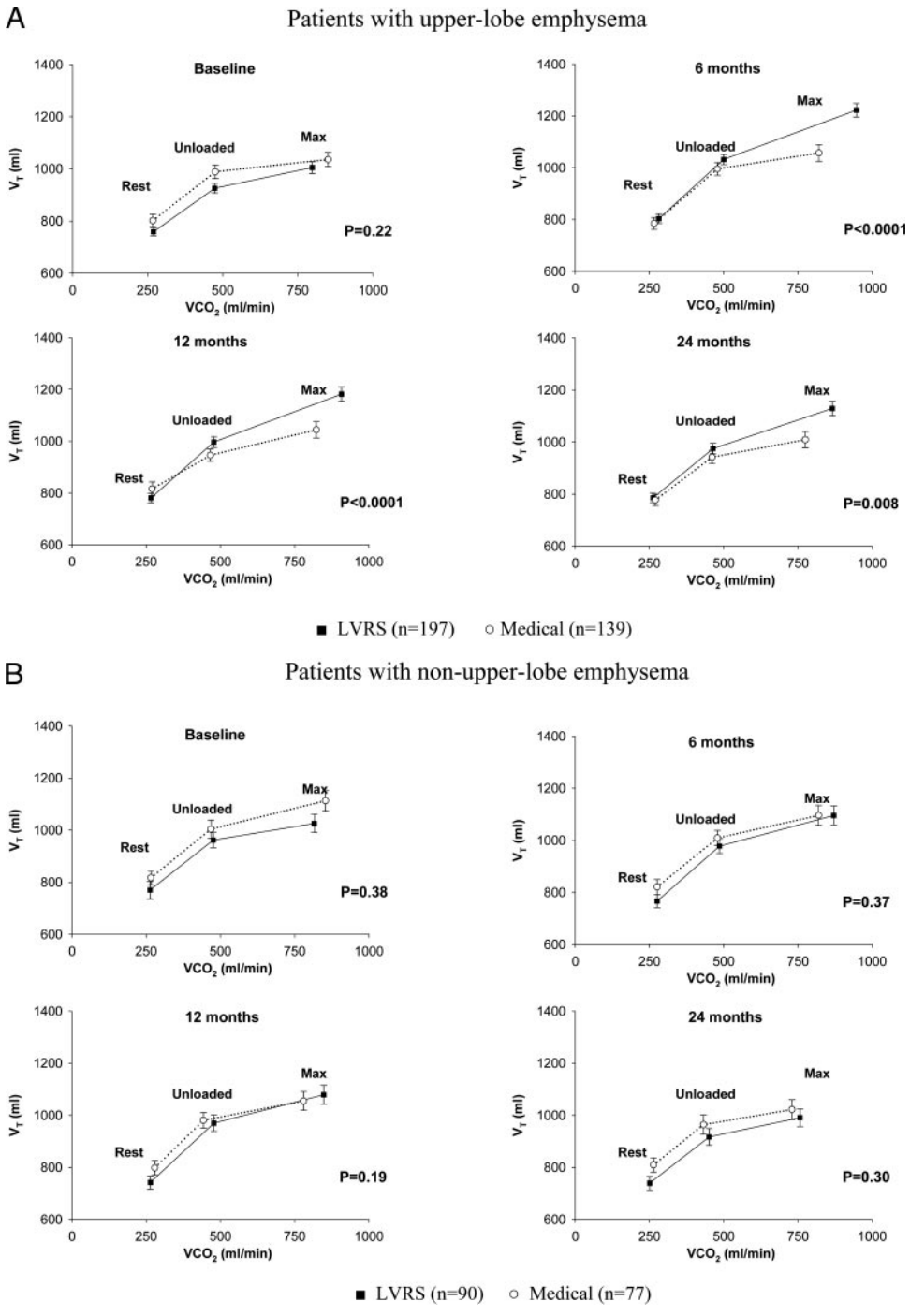

FIGURE 3. VT generation vs $\dot{V}CO_2$ at rest, unloaded cycling, and maximum exercise at baseline and 6, 12, and 24 months postrandomization to treatment, by chest CT scan pattern of emphysema, for substudy patients completing testing at all time points. Error bars show the VT SEM in each phase of testing.

Our data show that ventilatory improvements occur following LVRS throughout the continuum of exercise, from submaximal (unloaded cycling) through maximum symptom-limited exercise workloads. Although a submaximal study protocol was not used in this study, we measured all physiologic, ventilatory, and patient symptom scores during unloaded cycling, as well as at maximum exercise. This allowed us directly to observe physiologic improvements across the spectrum of exercise.

The improvement in ventilatory function during maximum exercise in patients treated with LVRS is most likely related to an increase in ventilatory capacity and decreased dead space. Post LVRS,

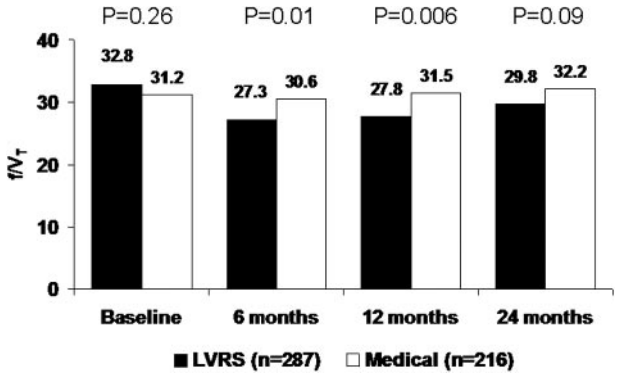

FIGURE 4. Rapid shallow breathing index (f/VT) at maximum exercise at baseline and 6, 12, and 24 months postrandomization to treatment, for patients completing testing at all time points.

patients exhibited higher VEmax and maximum VT during maximum exercise, as well as a reduction in the rapid shallow breathing index. These data suggest that ventilatory capacity was enhanced simultaneously with a reduction in an end-expiratory lung volume, suggesting a higher inspiratory capacity. Our data support others who showed a decrease in end-expiratory esophageal pressure[13,27] or an increase in inspiratory capacity[6] during exercise following LVRS.

Our data show that a decrease in ventilatory dead space occurs during unloaded cycling, as well as at maximum exercise following LVRS. When coupled with simultaneous increases in VEmax, the reductions in ventilatory dead space suggest an improvement in alveolar ventilation throughout the range of exercise, which resulted in improved carbon dioxide elimination.

The physiologic improvements we observed during unloaded cycling and maximum exercise were mirrored by reductions in their sensation of dyspnea. These data suggest that an improvement in ventilatory function is the major benefit of LVRS in terms of both exercise performance and symptoms.

The effect of the chest CT scan pattern of emphysema on influencing the changes in physiologic variables that we measured during maximum exercise is intriguing, but its mechanism is unclear. Patients with upper-lobe predominant emphysema had significant improvements in carbon dioxide elimination and their ability to generate VT across the spectrum of exercise, whereas those with non–upper-lobe predominant disease did not. Whether the CT scan pattern of emphysema is only a marker of patients with more severe airflow obstruction and gas trapping or truly influences the surgical consequences of LVRS is uncertain at present and requires further study.

Our study may be limited because the exercise substudy population was more likely to be male, slightly more hypoxemic at rest, had lower $PaCO_2$ values, and had more upper-lobe-predominant emphysema than the nonexercise substudy NETT cohort. However, we do not think these factors would negate any of the observed physiologic effects of LVRS on ventilatory mechanics during exercise for the general NETT emphysema patient population. Additionally, despite statistical significance, some of the mean changes in physiologic function post LVRS are small in magnitude (*eg*, $\dot{V}CO_2$, Borg scores for dyspnea and leg fatigue, and dead space) compared to the medically treated group. However, these mean changes in physiologic variables appear to be clinically meaningful because 20% of the LVRS patients group no longer had ventilatory limitation as a cause of exercise termination posttreatment.

Our data show that, following LVRS, patients with severe emphysema demonstrate an increase in exercise capacity, slower and deeper breathing, decreased ventilatory dead space, improved carbon dioxide elimination, a reduction in dyspnea, and less ventilatory limitation to perform maximum exercise. Additionally, the pattern of emphysema determined by CT scan inspection is associated with a change in breathing pattern and gas exchange during maximum exercise following LVRS.

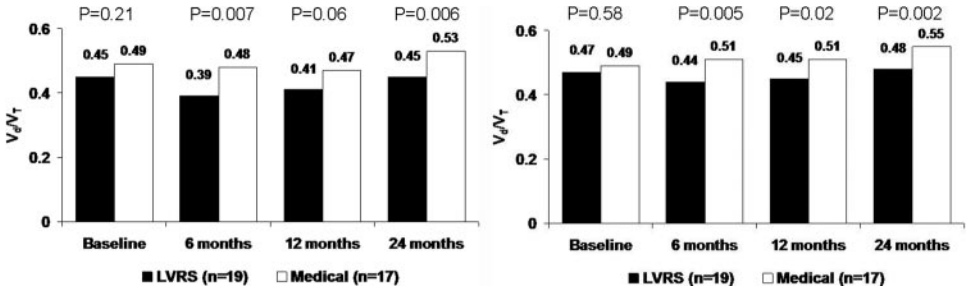

FIGURE 5. Physiologic dead space ventilation (VD/VT) at maximum exercise (*left*, *A*) and iso-workload (unloaded cycling) [*right*, *B*] at baseline and 6, 12, and 24 months postrandomization to treatment, for patients completing testing at all time points.

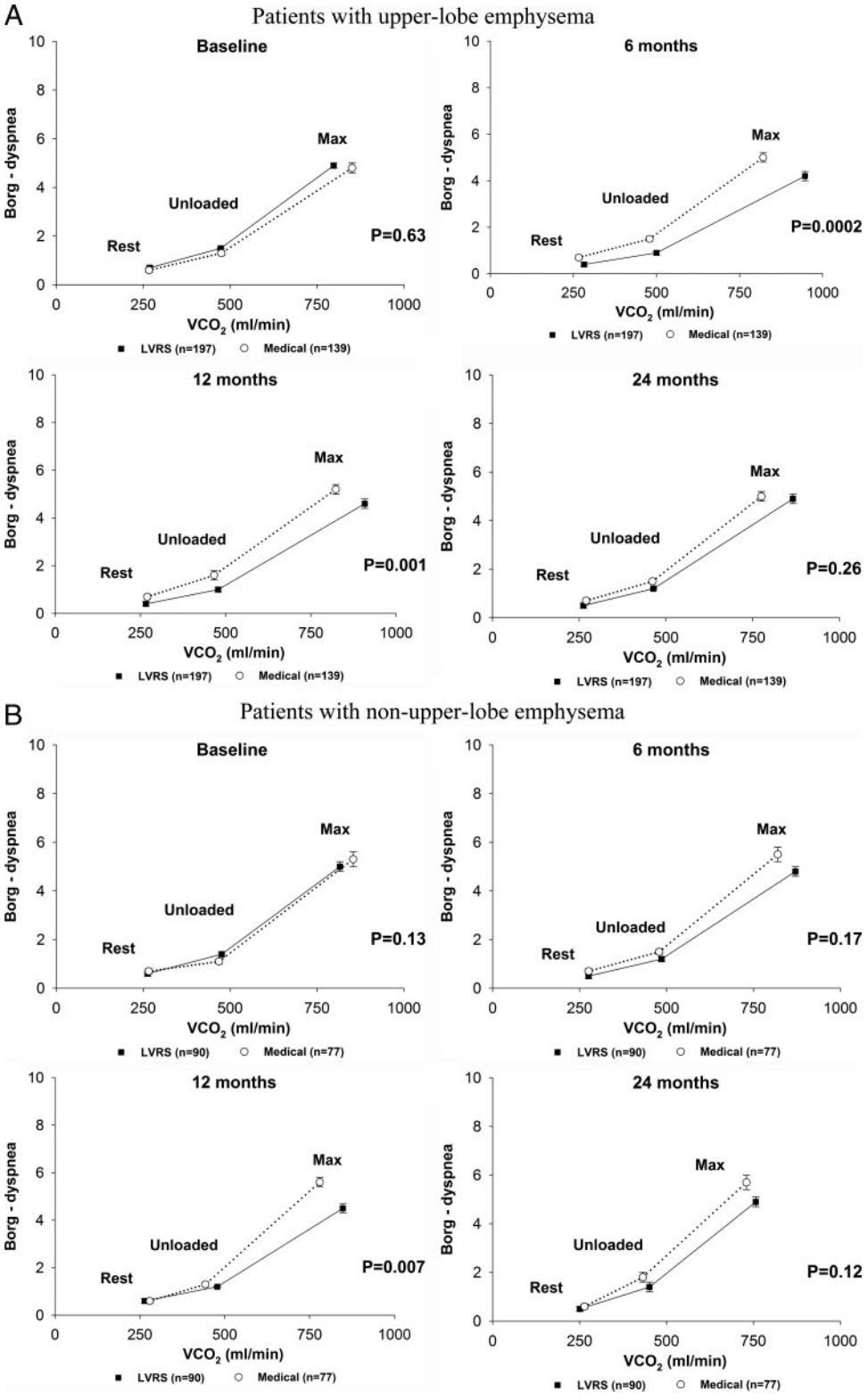

FIGURE 6. Relationship of Borg score rating of dyspnea to $\dot{V}CO_2$ during restful breathing, unloaded pedaling, and maximum exercise at baseline and 6, 12, and 24 months postrandomization to treatment, by chest CT scan pattern of emphysema, for patients completing testing at all time points. Error bars show the SEM Borg score rating of dyspnea in each phase of testing.

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