Weight Gain after Lung Reduction Surgery Is Related to Improved Lung Function and Ventilatory Efficiency

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***Rationale*: Lung volume reduction surgery (LVRS) is associated with weight gain in some patients, but the group that gains weight after LVRS and the mechanisms underlying this phenomenon have not been well characterized.**

***Objectives*: To describe the weight change profiles of LVRS patients enrolled in the National Emphysema Treatment Trial (NETT) and to correlate alterations in lung physiological parameters with changes in weight.**

***Methods*: We divided 1,077 non–high-risk patients in the NETT into groups according to baseline body mass index (BMI): underweight ($<$21 kg/m^2), normal weight (21–25 kg/m^2), overweight (25–30 kg/m^2), and obese ($>$30 kg/m^2). We compared BMI groups and LVRS and medical groups within each BMI stratum with respect to baseline characteristics and percent change in BMI (%ΔBMI) from baseline. We examined patients with (ΔBMI $\geqslant$ 5%) and without (ΔBMI $<$ 5%) significant weight gain at 6 months and assessed changes in lung function and ventilatory efficiency ($\dot{V}_E/\dot{V}_{CO_2}$).**

***Measurements and Main Results*: The percent change in BMI was greater in the LVRS arm than in the medical arm in the underweight and normal weight groups at all follow-up time points, and at 12 and 24 months in the overweight group. In the LVRS group, patients with ΔBMI $\geqslant$ 5% at 6 months had greater improvements in FEV_1 (11.53 $\pm$ 9.31 vs. 6.58 $\pm$ 8.68%; $P < 0.0001$), FVC (17.51 $\pm$ 15.20 vs. 7.55 $\pm$ 14.88%; $P < 0.0001$), residual volume (–66.20 $\pm$ 40.26 vs. –47.06 $\pm$ 39.87%; $P < 0.0001$), 6-minute walk distance (38.70 $\pm$ 69.57 vs. 7.57 $\pm$ 73.37 m; $P < 0.0001$), maximal expiratory pressures (12.73 $\pm$ 49.08 vs. 3.54 $\pm$ 32.22; $P = 0.0205$), and $\dot{V}_E/\dot{V}_{CO_2}$ (–1.58 $\pm$ 6.20 vs. 0.22 $\pm$ 8.20; $P = 0.0306$) at 6 months than patients with ΔBMI $<$ 5% at 6 months.**

***Conclusions*: LVRS leads to weight gain in nonobese patients, which is associated with improvement in lung function, exercise capacity, respiratory muscle strength, and ventilatory efficiency. These physiological changes may be partially responsible for weight gain in patients who undergo LVRS.**

Keywords: pulmonary disease; chronic obstructive; lung volume reduction surgery; ventilatory efficiency; cachexia

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Lung volume reduction surgery results in greater exercise capacity, improved lung function, and a reduction in mortality in selected patients with advanced emphysema compared with medical therapy. The impact of lung volume reduction surgery on body mass index has not been well described.

What This Study Adds to the Field

This study shows that underweight patients who underwent lung volume reduction surgery experienced significant improvements in body mass index, and that weight gain after lung volume reduction surgery was related to improved lung function and ventilatory efficiency. These physiological changes may be partially responsible for weight gain in patients who undergo lung volume reduction surgery.

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease with many associated comorbid disorders, including coronary heart disease, osteoporosis, metabolic syndrome, and low body mass index (BMI) (1, 2). The abnormal local inflammatory response to cigarette smoke leads to airflow obstruction and also results in systemic inflammation, characterized by increased levels of IL-6, IL-8, tumor necrosis factor (TNF)-α, and C-reactive protein (3); this systemic inflammation is believed to be responsible for accelerated bone loss, premature development of atherosclerotic heart disease, and skeletal muscle apoptosis (1, 2). A low BMI is also a result of several other factors, including breathlessness while eating, difficulty preparing meals because of breathlessness, derangement of glycolipemic hormone metabolism, higher resting energy expenditure from increased work of breathing, physical deconditioning, and respiratory cachexia (4–6).

Low BMI has been shown to be a risk factor for mortality in COPD, both independently as well as a part of a multidimensional index (7–9). Lung volume reduction surgery (LVRS) has been shown to decrease mortality in select patients with advanced emphysema (10) and may improve systemic inflammation and nutritional status (6, 11). In whom LVRS will cause weight gain and the mechanisms responsible are currently not well characterized.

We sought to describe the weight change profiles of LVRS patients enrolled in the National Emphysema Treatment Trial (NETT). We also correlated alterations in lung physiological parameters with changes in weight. We hypothesized that patients who were more underweight would gain more weight after LVRS, and that weight gain would be associated with improvements in lung function and ventilatory efficiency. Some of these data were

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* A complete list of members, participating clinical centers, and other participants may be found before the beginning of the REFERENCES.

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reported in an abstract at the 2009 American Thoracic Society International Conference (12).

METHODS

Patient Selection

Enrollment criteria for NETT have been previously described (10). All patients provided written informed consent, and the study was approved by the institutional review board at each center. Inclusion criteria included a physical examination consistent with emphysema, radiographic evidence of bilateral emphysema on high-resolution computed tomography (HRCT) scan, FEV_1 not exceeding 45% predicted, but at least 15% of predicted if age 70 years or older, total lung capacity (TLC) equal to or greater than 100% predicted, RV equal to or greater than 150% predicted, P_{CO_2} not greater than 60 mm Hg, P_{O_2} equal to or greater than 45 mm Hg on room air, and a postrehabilitation 6-minute walk distance greater than 140 m. Patients also needed to be stable on not more than 20 mg of prednisone per day, nonsmoking for 4 months, and have a BMI not greater than 31.1 kg/m^2 in men and not greater than 32.3 kg/m^2 in women. All patients underwent 6–10 weeks of pulmonary rehabilitation, and then were randomized to either LVRS or continued medical therapy per American Thoracic Society guidelines. Baseline measurements of pulmonary function, 6-minute walk distance, and health-related quality of life obtained from the St. George's Respiratory Questionnaire (SGRQ) were obtained after completing pulmonary rehabilitation but before randomization, and again at 6, 12, 24, and 36 months.

Patients considered at high risk for LVRS (13) were excluded, and one additional patient without BMI data at baseline was excluded. We divided the remaining 1,077 non–high-risk patients into four groups based on baseline BMI (after pulmonary rehabilitation and before randomization to either LVRS or medical therapy): underweight (<21 kg/m^2), normal weight (21–25 kg/m^2), overweight (25–30 kg/m^2), and obese (>30 kg/m^2). We compared the BMI groups with respect to baseline characteristics. We also stratified on BMI group and compared the LVRS and medical groups with respect to baseline characteristics and percent change in BMI (%ΔBMI) from baseline to follow-up at 6, 12, 24, and 36 months.

Stratifying by treatment arm, those with significant weight gain from baseline to 6 months (an increase in BMI $\geq$ 5%, ΔBMI $\geq$ 5%) were compared with those without significant weight gain (no change, a decrease, or an increase in BMI < 5%, ΔBMI < 5%) with respect to changes from baseline to 6 months in lung function, SGRQ score, ventilatory efficiency, and 6-minute walk distance. ΔBMI equal to or greater than 5% was chosen as significant because of existing data suggesting that a change in BMI of 5% is clinically significant (14, 15). Ventilatory efficiency was defined as the ratio of minute ventilation ($\dot{V}_E$) to carbon dioxide production ($\dot{V}_{CO_2}$) (16) during unloaded pedaling (chosen as an iso-study time point) during incremental cardiopulmonary exercise testing. Change in diffusing capacity of carbon monoxide (D_{LCO}) was assessed at 12 months because this lung function parameter was not assessed at 6 months.

Statistical Analysis

Statistics were performed with JMP 8.0 (SAS, Cary, NC) or SAS 9.2 (SAS). Descriptive statistics are reported as means ± SD, except where otherwise noted. A P value less than 0.05 was considered statistically significant. An unpaired t test was used to compare baseline demographic and pulmonary function data between BMI groups and between LVRS and medical patients. In each BMI group, LVRS and medical patients were compared on %ΔBMI from baseline to each follow-up time point, using unpaired t tests. Within each treatment group, changes in lung function, ventilatory efficiency, 6-minute walk distance, and SGRQ scores were compared between those with ΔBMI equal to or greater than 5% and those with ΔBMI less than 5%, using unpaired t tests. Multivariate logistic regression was performed to assess the independent effects of treatment arm (LVRS vs. medical therapy), sex, and baseline exercise category (low vs. high exercise), BMI group, lung function, and $\dot{V}_E/\dot{V}_{CO_2}$ on ΔBMI equal to or greater than 5% at 6 months.

RESULTS

There were 182, 391, 391, and 113 patients in the underweight, normal weight, overweight, and obese BMI groups, respectively (total n = 1,077). Baseline data are listed in Table 1. Racial distribution was not different between BMI groups. The underweight group was composed of fewer males compared with the normal weight and overweight groups (45 vs. 62, 65%, respectively; both $P < 0.05$). The underweight group had lower percent

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS IN EACH BODY MASS INDEX STRATUM

	Underweight (BMI < 21)			Normal Weight (BMI 21–25)			Overweight (BMI 25–30)			Obese (BMI > 30)		
	All (*n* = 182)	LVRS (*n* = 97)	MED (*n* = 85)	All (*n* = 391)	LVRS (*n* = 207)	MED (*n* = 184)	All (*n* = 391)	LVRS (*n* = 176)	MED (*n* = 215)	All (*n* = 113)	LVRS (*n* = 158)	MED (*n* = 55)
Age, yr	68 ± 6*	68 ± 6	68 ± 5	68 ± 6*†	67 ± 7	67 ± 6	67 ± 6	67 ± 7	67 ± 7	66 ± 6	66 ± 6	66 ± 6
Sex, % male	45†‡	38	52	62	60	64	65	64	66	57	50	64
Race, % white	93	93	94	94	96	92	96	96	96	96	97	96
FVC, %pred	67 ± 16*†‡	66 ± 16	68 ± 16	70 ± 15	70 ± 14	70 ± 15	69 ± 15	69 ± 16	69 ± 14	70 ± 14	70 ± 14	71 ± 14
FEV_1, %pred	27 ± 7*	27 ± 7	27 ± 6	28 ± 6*	28 ± 6	28 ± 7	28 ± 7*	28 ± 7	28 ± 6	30 ± 7	30 ± 7	30 ± 7
TLC, %pred	131 ± 15*†‡	131 ± 16	131 ± 14	127 ± 14	128 ± 15	127 ± 13	127 ± 15	126 ± 14	128 ± 15	125 ± 14	125 ± 15	124 ± 13
RV, %pred	226 ± 46*†‡	226 ± 43	227 ± 48	215 ± 43	214 ± 45	216 ± 40	215 ± 47	212 ± 47	217 ± 47	207 ± 41	207 ± 45	206 ± 37
Pa_{O_2}, mm Hg	64 ± 11‡	64 ± 11	64 ± 10	66 ± 11	67 ± 11	66 ± 10	64 ± 10‡	64 ± 10	64 ± 10	62 ± 9‡	61 ± 8	64 ± 10
Pa_{CO_2}, mm Hg	43 ± 6‡	43 ± 6	43 ± 6	42 ± 5	42 ± 5	42 ± 5	43 ± 6‡	43 ± 6	43 ± 6	44 ± 5‡	44 ± 5	44 ± 5
D_{LCO}, %pred	26 ± 8*†‡	26 ± 9	25 ± 8	28 ± 9*†	29 ± 9	28 ± 8	31 ± 9*	30 ± 9	31 ± 10	33 ± 10	32 ± 10	35 ± 10
6MWD, m	366 ± 87†‡	374 ± 88	357 ± 85	385 ± 96*†§	383 ± 97	387 ± 95	379 ± 93	376 ± 92	382 ± 94	353 ± 96	347 ± 88	358 ± 104
$\dot{V}_E/\dot{V}_{CO_2}$	46.0 ± 12.8*†‡	47.5 ± 13.3	44.2 ± 12.0	43.5 ± 10.9*†	43.1 ± 12.0	44.0 ± 9.6	41.4 ± 8.5*	40.9 ± 8.1	41.9 ± 8.7	38.8 ± 8.1	37.1 ± 8.3‖	40.5 ± 7.7
SGRQ	55 ± 12†‡	55 ± 12	56 ± 12	51 ± 13	50 ± 13	53 ± 13	52 ± 13	53 ± 13	52 ± 12	54 ± 13	52 ± 11	55 ± 14
UL, %	61.5	60.8	62.4	65.0	65.7	64.1	67.8	63.6	71.2	69.0	65.5	72.7
Low Ex, %	61.0*†‡	66.0	55.3	39.9	41.6	38.0	34.8	30.7	38.1	31.9	32.8	30.9
ULLE, %	39.6*†‡	43.3	35.3	26.6	26.1	27.2	22.8	17.6	27.0‖	22.1	20.7	23.6
BMI, kg/m^2	19.4 ± 1.2*†‡	19.4 ± 1.3	19.3 ± 1.2	23.2 ± 1.1*†	23.2 ± 1.2	23.2 ± 1.1	27.2 ± 1.4*	27.2 ± 1.4	27.0 ± 1.4	30.9 ± 0.7	31.1 ± 0.8	30.8 ± 0.6

Definition of abbreviations: %pred = percentage of predicted value; 6MWD = 6-minute walk distance; BMI = body mass index; D_{LCO} = diffusing capacity of carbon monoxide; Low Ex = low-exercise group (≤40 W on cardiopulmonary exercise test for males, ≤25 W for females); LVRS = lung volume reduction surgery; MED = medical treatment arm; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; TLC = total lung capacity; UL = upper lobe–predominant emphysema; ULLE = upper lobe–predominant emphysema and low-exercise subgroup; $\dot{V}_E/\dot{V}_{CO_2}$ = ventilatory efficiency.

* $P < 0.05$ compared with obese.

† $P < 0.05$ compared with overweight.

‡ $P < 0.05$ compared with normal weight.

§ $P < 0.05$ compared with underweight.

‖ $P < 0.05$ LVRS versus MED within BMI stratum.

predicted FEV_1 compared with the other three BMI groups (27 ± 7 vs. 28 ± 6, 28 ± 7, and 30 ± 7% predicted in the normal weight, overweight, and obese groups, respectively; all $P < 0.05$) as well as a lower percent predicted FVC (67 ± 16 vs. 70 ± 15, 69 ± 15, 70 ± 14% predicted, respectively; all $P < 0.05$), a higher percent predicted TLC (131 ± 15 vs. 127 ± 14, 127 ± 15, 125 ± 14% predicted, respectively; all $P < 0.05$), a higher percent predicted RV (226 ± 46 vs. 215 ± 43, 215 ± 47, 207 ± 41% predicted, respectively; all $P < 0.05$), and a lower percent predicted D_{LCO} (26 ± 8 vs. 28 ± 9, 31 ± 9, 33 ± 10% predicted, respectively; all $P < 0.05$). The underweight group also had higher SGRQ scores compared with the other BMI groups (55 ± 12 vs. 51 ± 13, 52 ± 13, 54 ± 13, respectively; all $P < 0.05$), higher $\dot{V}_E/\dot{V}_{CO_2}$ during unloaded pedaling (46.0 ± 12.8 vs. 43.5 ± 10.9, 41.4 ± 8.5, 38.8 ± 8.1, respectively; all $P < 0.05$), and a greater percentage of patients categorized as low exercise capacity (≤40 W for men and ≤25 W for women on incremental cardiopulmonary exercise testing; 61.0 vs. 39.9, 34.8, 31.9%; all $P < 0.05$). All groups had comparable percentages of patients with upper lobe–predominant emphysema on CT scan. Overall, the underweight group had a higher percentage of the upper lobe–predominant emphysema/low-exercise capacity subgroup, as defined by NETT (10) (39.6 vs. 26.6, 22.8, 22.1%, respectively; all $P < 0.05$).

Changes in BMI in each BMI group are listed in Table 2 and displayed in Figure 1. BMI remained relatively stable in all weight groups in medically treated patients. %ΔBMI was significantly higher in the LVRS arm compared with the medical arm in the underweight and normal weight groups at all follow-up time points. In the overweight group, %ΔBMI was significantly higher in the LVRS arm at 12 and 24 months compared with the medical arm. There were no significant differences between LVRS and medical arms in the obese group. The differences in %ΔBMI between LVRS and medical arms were greatest in the underweight group compared with other BMI groups, and the mean BMI change from baseline progressively increased in the underweight group at 12, 24, and 36 months. The underweight and normal weight groups had a significantly higher percentage of patients in the LVRS arm who had a significant increase in BMI (ΔBMI ⩾ 5%) at 6 months compared with the medical arm (*see* Figure 2).

Table 3 and Figure 3 summarize the changes in physiological parameters, gas exchange, walk distance, health-related quality of life, and ventilator efficiency in patients who had a significant increase in BMI (ΔBMI ⩾ 5%) and those who did not (ΔBMI < 5%) at 6 months, stratified by treatment. Overall, 24.7% of the LVRS group had a ΔBMI of at least 5%, whereas only 10.3% of the MED group had a ΔBMI of at least 5%. Compared with the LVRS ΔBMI < 5% group, the LVRS ΔBMI ⩾ 5% group had greater improvements in percent predicted FEV_1 (11.53 ± 9.31 vs. 6.58 ± 8.68%; $P < 0.0001$), FVC (17.51 ± 15.20 vs. 7.55 ± 14.88%; $P < 0.0001$), and RV (–66.20 ± 40.26 vs. –47.06 ± 39.87%; $P < 0.0001$). Similarly, the LVRS ΔBMI ⩾ 5% group compared with the LVRS ΔBMI < 5% group had greater improvements in 6-minute walk distance (38.70 ± 69.57 vs. 7.57 ± 73.37 m; $P < 0.0001$), Pa_{CO_2} (–2.80 ± 5.02 vs. –1.70 ± 4.66 mm Hg; $P = 0.0300$), Pa_{O_2} (7.48 ± 9.18 vs. 3.73 ± 9.41 mm Hg; $P < 0.0002$), and SGRQ scores (–15.30 ± 14.08 vs. –9.15 ± 14.44; $P < 0.0001$). Changes in maximal expiratory pressures (12.73 ± 49.08 vs. 3.54 ± 32.22; $P = 0.0205$) were greater in the LVRS ΔBMI ⩾ 5% group compared with the LVRS ΔBMI < 5% group. $\dot{V}_E/\dot{V}_{CO_2}$ decreased at 6 months in the LVRS ΔBMI ⩾ 5% group, whereas in the LVRS ΔBMI < 5% group the $\dot{V}_E/\dot{V}_{CO_2}$ increased (–1.58 ± 6.20 vs. 0.22 ± 8.20; $P = 0.0306$). There were no significant differences in changes from baseline in the aforementioned parameters in the MED ΔBMI ⩾ 5% group compared with the MED ΔBMI < 5% group, with the exception of 6-minute walk distance, which decreased more in the MED ΔBMI ⩾ 5% group and in the MED ΔBMI < 5% group (–46.98 ± 8.18 vs. –21.34 ± 2.78; $P = 0.0032$).

In multivariate analysis using a binary logistic regression model of ΔBMI equal to or greater than 5% on treatment arm (LVRS vs. medical), sex, exercise category (low- vs. high-exercise capacity), upper lobe predominance (vs. other), baseline lung function, baseline $\dot{V}_E/\dot{V}_{CO_2}$, and BMI group, the LVRS arm (vs. MED) and the underweight group (vs. normal) were significantly associated with a ΔBMI equal to or greater than 5% (odds ratio [OR], 2.70; 95% confidence interval [CI], 1.81–4.04; and OR, 2.36; 95% CI, 1.39–4.01, respectively). Baseline FVC was inversely associated with ΔBMI equal to or greater than 5% (OR, 0.97; 95% CI, 0.95–0.99). Sex and baseline exercise category, FEV_1, TLC, RV, and $\dot{V}_E/\dot{V}_{CO_2}$ were not significantly associated with ΔBMI equal to or greater than 5% (*see* Table 4).

DISCUSSION

We showed in a large group of well-characterized patients with advanced emphysema that LVRS was more likely to be associated with significant weight gain, whereas medical therapy alone had little effect on weight. Using preoperative BMI, we were also

TABLE 2. PERCENT CHANGE IN BODY MASS INDEX (BMI) OVER TIME WITHIN BASELINE BMI GROUP

	Underweight (BMI < 21)			Normal Weight (BMI 21–25)			Overweight (BMI 25–30)			Obese (BMI > 30)		
	LVRS (*n = 97*)	MED (*n = 85*)	*P* Value	LVRS (*n = 207*)	MED (*n = 184*)	*P* Value	LVRS (*n = 176*)	MED (*n = 215*)	*P* Value	LVRS (*n = 58*)	MED (*n = 55*)	*P* Value
6 mo	4.13 ± 8.65 (n = 79)	0.89 ± 4.82 (n = 51)	**0.0164**	1.67 ± 6.02 (n = 169)	−0.42 ± 3.79 (n = 140)	**0.0004**	−0.20 ± 6.34 (n = 150)	−0.14 ± 4.38 (n = 160)	0.9276	0.25 ± 6.30 (n = 45)	2.23 ± 3.62 (n = 44)	0.0735
12 mo	6.70 ± 9.76 (n = 70)	2.25 ± 6.02 (n = 44)	**0.0077**	3.30 ± 7.69 (n = 141)	−0.45 ± 5.61 (n = 115)	**<0.0001**	2.37 ± 8.07 (n = 131)	−0.19 ± 5.77 (n = 136)	**0.0029**	2.72 ± 6.87 (n = 41)	1.47 ± 5.49 (n = 34)	0.3915
24 mo	8.25 ± 11.62 (n = 60)	1.21 ± 7.60 (n = 25)	**0.0066**	4.07 ± 7.84 (n = 121)	0.58 ± 7.59 (n = 95)	**0.0012**	3.32 ± 8.52 (n = 110)	−0.45 ± 6.89 (n = 116)	**0.0003**	4.69 ± 8.08 (n = 35)	1.25 ± 6.33 (n = 28)	0.0695
36 mo	9.05 ± 12.14 (n = 32)	0.85 ± 7.64 (n = 16)	**0.0117**	3.28 ± 8.67 (n = 77)	-0.32 ± 8.44 (n = 55)	**0.0188**	3.43 ± 9.10 (n = 67)	0.97 ± 6.95 (n = 64)	0.0859	3.48 ± 9.65 (n = 25)	2.46 ± 7.44 (n = 14)	0.7352
% of each group with ΔBMI ⩾ 5% at 6 mo	37.97	17.65	**0.0182**	23.67	3.57	**<0.0001**	18.00	11.88	0.1510	22.22	18.18	0.7928

Definition of abbreviations: BMI = body mass index; LVRS = lung volume reduction surgery; MED = medical treatment arm.

All data are expressed as means ± SD, except percentage of each group with ΔBMI equal to or greater than 5% at 6 months. *P* values are for differences between LVRS and MED within the BMI group.

Bold indicates *P* values less than 0.05, the level of statistical significance.

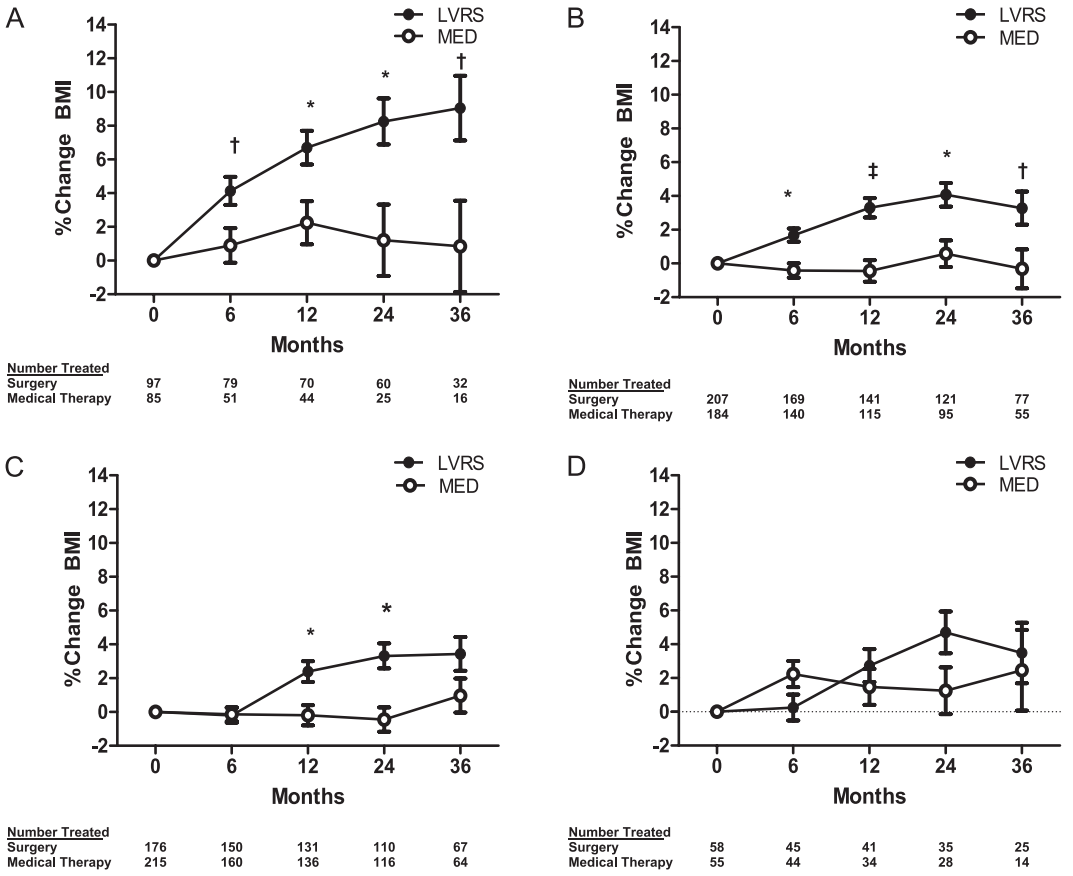

Figure 1. Percent change in body mass index by treatment group and body mass index (BMI) group: (*A*) underweight, (*B*) normal weight, (*C*) overweight, and (*D*) obese. *Solid circles* represent patients in the lung volume reduction surgery (LVRS) group, and *open circles* represent patients in the medical therapy (MED) group. Data present means ± SE. *$P < 0.01$, †$P < 0.05$, ‡$P <$ 0.0001 for LVRS versus MED.

able to identify patient groups more likely to gain weight, as well as their associated changes in lung function and ventilatory efficiency. Significant weight gain was accomplished in those who were not obese at baseline, and these effects were independent of preoperative exercise subgroup and distribution of emphysema on CT scan, which were primary predictors of outcome in the NETT. The changes in BMI were most profound in the underweight group, followed by the normal weight and overweight groups. In addition, the underweight group continued to gain weight through 36 months of follow-up, whereas the normal weight and overweight groups achieved a plateau of weight gain at 24 months. In the LVRS arm, those who experienced significant weight gain had greater improvements in spirometry, respiratory muscle strength, lung volumes, ventilatory efficiency, health-related quality of life, and 6-minute walk distance compared with those without a significant weight gain. Therefore, we posit that these changes in lung physiology exert a positive effect on BMI by improving exercise capacity, with a resultant increase in muscle mass and a reduction of resting energy expenditure (REE).

What defines a significant weight change is a matter of debate. In the elderly population, involuntary weight loss of 5% in 6 months is associated with increased mortality (14), and intentional weight loss of 5% in the obese population significantly reduces cardiovascular risk (15). However, in the underweight population, it is unclear how much weight gain is necessary to have a significant impact on outcome. A prospective study of an aggressive nutritional support program in 203 patients with COPD has shown that a weight gain of 2 kg over 8 weeks in nutritionally depleted patients was associated with improvement in long-term outcomes (7). In addition, a small study of 30 LVRS patients revealed that a 5% increase in BMI was associated with improved health-related quality of life, dyspnea scores, and lung function (17). On the basis of these data, we chose a threshold of a 5% increase in BMI in 6 months to be considered clinically significant for our analysis.

Cachexia is a common systemic manifestation of COPD, affecting 20–35% of patients (18, 19). The underlying mechanisms are unclear, but multiple factors have been implicated, including increased REE (4, 20), elevated systemic inflammation (5), derangement of anabolic hormone metabolism (21, 22), and muscle disuse atrophy. Sergi and colleagues found that REE was 10% higher in patients with COPD than in normal subjects

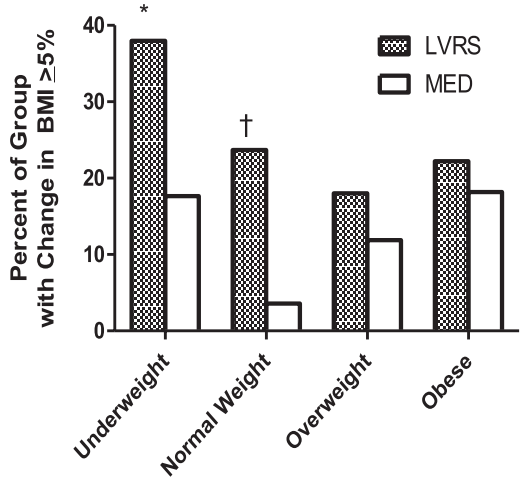

Figure 2. Percentage of each body mass index (BMI) group with an increase in BMI of at least 5% at 6 months after randomization to lung volume reduction surgery (LVRS) or medical therapy (MED). *$P < 0.05$, †$P < 0.0001$ for LVRS versus MED.

TABLE 3. CHANGES IN LUNG FUNCTION, RESPIRATORY MUSCLE STRENGTH, 6-MINUTE WALK DISTANCE, RESTING GAS EXCHANGE, HEALTH-RELATED QUALITY OF LIFE, AND VENTILATORY EFFICIENCY STRATIFIED BY TREATMENT GROUP AND CHANGE IN BODY MASS INDEX AT 6 MONTHS IN 900 PATIENTS SURVIVING AT 6 MONTHS

	LVRS			MED		
Variable	ΔBMI ⩾ 5% (*n* = 117)	ΔBMI < 5% (*n* = 357)	*P* Value	ΔBMI ⩾ 5% (*n* = 44)	ΔBMI < 5% (*n* = 382)	*P* Value
FEV_1, %pred	11.53 ± 9.31	6.58 ± 8.68	**<0.0001**	−0.59 ± 4.63	−0.38 ± 4.27	0.7622
FVC, %pred	17.51 ± 15.20	7.55 ± 14.88	**<0.0001**	−2.05 ± 9.21	−1.44 ± 10.09	0.6091
RV, %pred	−66.20 ± 40.26	−47.06 ± 39.87	**<0.0001**	−4.82 ± 36.93	1.78 ± 29.63	0.1740
TLC, %pred	−16.30 ± 11.84	−14.46 ± 13.17	0.1797	−2.11 ± 10.31	−0.29 ± 10.23	0.2640
D_{LCO}, %pred	4.10 ± 9.10	1.44 ± 8.34	**0.0100**	−1.23 ± 5.80	−2.01 ± 6.68	0.5108
MIP, %pred	25.20 ± 38.34	18.43 ± 33.93	0.0706	6.62 ± 23.48	0.80 ± 31.26	0.2326
MEP, %pred	12.73 ± 49.08	3.54 ± 32.22	**0.0205**	9.56 ± 37.41	0.87 ± 30.32	0.0834
6MWD, m	38.70 ± 69.57	7.57 ± 73.37	**<0.0001**	−46.98 ± 8.18	−21.34 ± 2.78	**0.0032**
Pa_{CO_2}, mm Hg	−2.80 ± 5.02	−1.70 ± 4.66	**0.0300**	1.11 ± 3.21	0.65 ± 3.69	0.4245
Pa_{O_2}, mm Hg	7.48 ± 9.18	3.73 ± 9.41	**0.0002**	−1.68 ± 8.83	1.22 ± 6.98	0.6864
SGRQ	−15.30 ± 14.08	−9.15 ± 14.44	**<0.0001**	2.83 ± 8.13	1.92 ± 10.49	0.5806
$\dot{V}_E/\dot{V}_{CO_2}$	−1.58 ± 6.20	0.22 ± 8.20	**0.0306**	−1.73 ± 5.05	0.03 ± 8.02	0.1610

Definition of abbreviations: 6MWD = 6-minute walk distance; BMI = body mass index; D_{LCO} = diffusing capacity of carbon monoxide; LVRS = lung volume reduction surgery; MED = medical treatment arm; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; TLC = total lung capacity; $\dot{V}_E/\dot{V}_{CO_2}$ = ventilatory efficiency.

All values are expressed as means ± SD. All data were reported at 6 months of follow-up, except for D_{LCO}, which was determined at 12 months. Bold indicates *P* values less than 0.05, the level of statistical significance.

similar in age, height, and weight (20). Similarly, Schols and colleagues found that REE, when adjusted for fat-free mass, was higher in patients with COPD who lost weight compared with those whose weight remained stable (23). Serum levels of TNF-α are higher in cachectic patients with COPD compared with noncachectic patients with COPD and healthy control subjects (24, 25), and elevations in IL-1 and IL-6 may also play a role in the development of cachexia (26, 27). Reductions in circulating levels of testosterone, growth hormone, insulin-like growth factor, and leptin have also been found in cachectic patients with COPD (21, 22, 25).

LVRS has numerous beneficial effects on metabolism and systemic inflammation, and can potentially reduce the processes leading to cachexia in COPD. In a study of 30 LVRS and 22 pulmonary rehabilitation patients, the LVRS group had an 8% decrease in REE adjusted for fat-free mass, compared with the rehabilitation group, which had in increase of 4.2% (17). There was also a profound decrease in respiratory muscle oxygen consumption by 44.1%, which correlated well with decreases in RV after surgery. Another study of 28 LVRS patients found significant reductions in serum levels of TNF-α, IL-6, and IL-8 after surgery, which again correlated with reductions in RV (11). Similarly, in 33 LVRS patients, the reduction in RV correlated with increases in serum ghrelin (an appetite-stimulating hormone), decreases in serum leptin (a fat-burning hormone and appetite suppressant), and increases in fat-free mass (6). In addition, all these studies demonstrated weight gain after LVRS. One study found that the reduction in RV after LVRS not only correlated with increases in BMI but was also related to improved pulmonary and cardiovascular outcomes (28). Therefore, it seems that the reduction in hyperinflation from lung volume reduction is a major mechanism responsible for the reduction in energy expenditure, systemic inflammation, and anabolic hormone metabolism, and weight gain seen after LVRS.

However, these studies involved small numbers of patients with primarily low baseline BMI (mean BMI approximately 22 to 23 kg/m^2 across studies). As in prior studies, our study shows that reduction in residual volume was greater in those with significant weight gain, supporting the notion that the reduction in air trapping leads to decreased systemic inflammation and reduced REE. Unlike other studies, our study involved the analysis of 1,077 patients with a wide range of BMI, and is the first to stratify changes in weight according to baseline BMI. We also found weight gain in those who were normal weight and overweight, but not in those who were obese. The greatest increases in BMI occurred in the underweight group, suggesting that REE and systemic inflammation are highest in this group, which was more profoundly affected by LVRS.

An important contribution of our study is the demonstration of improvements in ventilatory efficiency and respiratory muscle strength in those who had significant weight gain. Ventilatory efficiency, defined as the ratio of minute ventilation to carbon dioxide production (16), has been shown to have prognostic value in heart failure and several pulmonary diseases (29, 30). At rest or during mild exercise, $\dot{V}_E/\dot{V}_{CO_2}$ can vary widely depending on Pa_{CO_2}, anxiety, breathing pattern, ventilation–perfusion

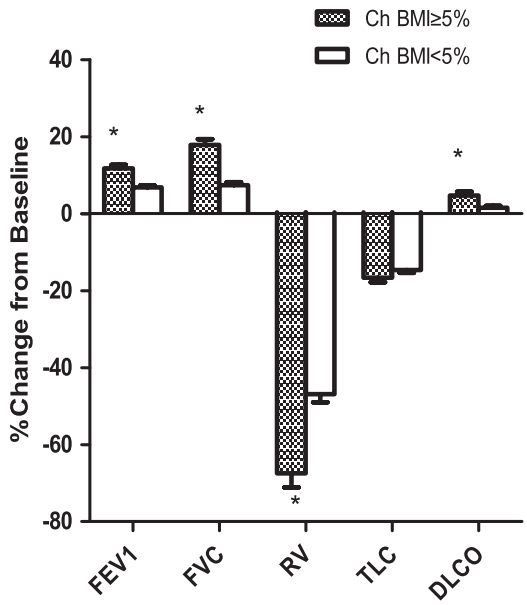

Figure 3. Change in body mass index (BMI) at 6 months and percent changes in lung function measures from baseline to 6 months (except the diffusing capacity of carbon monoxide [D_{LCO}], which was assessed at 12 mo). *Shaded columns* represent patients who had an increase in BMI of at least 5% at 6 months, and *open columns* represent patients with a change in BMI less than 5%. Data represent the lung volume reduction surgery (LVRS) treatment group and are expressed as means ± SE. *$P <$ 0.0001 for ΔBMI ⩾ 5% versus ΔBMI < 5%.

TABLE 4. ADJUSTED ODDS RATIOS IN MULTIVARIATE ANALYSIS FOR CHANGE IN BODY MASS INDEX OF AT LEAST 5% AT 6 MONTHS IN 837 NON–HIGH-RISK PATIENTS SURVIVING TO 6 MONTHS

Variable	OR	95% CI	*P* Value	*P* Value for Combination of Factors
LVRS vs. MED	2.70	1.81, 4.04	**<0.0001**	
Female vs. male	0.79	0.50, 1.25	0.2998	
Low exercise vs. high exercise	0.93	0.61, 1.41	0.7194	
UL predominant vs. other	1.48	0.98, 2.25	0.0651	
Underweight vs. normal	2.36	1.39, 4.01	**0.0015**	**0.0057**
Overweight vs. normal	1.02	0.64, 1.62	0.9301	
Obese vs. normal	1.52	0.80, 2.90	0.2015	
Baseline FVC, % predicted	0.97	0.95, 0.99	**0.0019**	
Baseline FEV_1, % predicted	1.03	0.99, 1.07	0.2174	
Baseline TLC, % predicted	1.02	0.99, 1.05	0.1522	
Baseline RV, % predicted	1.00	0.99, 1.01	0.7202	
Baseline $\dot{V}_E/\dot{V}_{CO_2}$	1.00	0.98, 1.01	0.6479	

Definition of abbreviations: CI = confidence interval; LVRS = lung volume reduction surgery; MED = medical treatment arm; OR = odds ratio; RV = residual volume; TLC = total lung capacity; UL = upper lobe; $\dot{V}_E/\dot{V}_{CO_2}$ = ventilatory efficiency.

Bold indicates *P* values less than 0.05, the level of statistical significance.

matching, underlying metabolic demand, and ratio of dead space to tidal volume (V_D/V_T) (31). The observed reductions of $\dot{V}_E/\dot{V}_{CO_2}$ after LVRS may be due to decreases in V_D/V_T, alterations in breathing pattern, and a fall in resting Pa_{CO_2} (32). These improvements in ventilatory efficiency may explain the decreases in REE, thereby leading to a gain in weight for a given caloric input.

Although this is the largest analysis of changes in BMI after LVRS, some limitations should be acknowledged. This study involved a select group of patients with advanced emphysema, with a post-hoc breakdown of patients into groups based on their BMI at baseline. In addition, incomplete follow-up is a weakness of our data set. Two hundred and forty (22%) of the 1,077 patients in our study population did not have data at 6 months, either due to death in the first 6 months of follow-up (53 patients) or because they did not return for the 6-month visit (187 patients), possibly due to declining health or for some reason unrelated to health. An analysis assuming that all those who missed the 6-month visit (due to death or other reason) were in the $\Delta BMI < 5\%$ group gave results consistent with our primary results. An analysis assuming those who died before 6 months were in the $\Delta BMI < 5\%$ group and that those who missed the visit for other reasons were in the $\Delta BMI \geq 5\%$ group gave results that were partially consistent with the primary results; in this analysis, LVRS and medical patients had similar odds of weight gain. Although our assumptions were extreme given the unequal proportions in the LVRS and medical groups of patients with ΔBMI equal to or greater than 5%, it is possible that loss to follow-up affected our findings.

Another limitation is that because only BMI was measured, it is not clear that the observed weight gain is due to cachexia reversal in these patients. Indeed, weight gain was seen in those who were normal weight or overweight, two groups that are less likely to have muscle cachexia. However, the significant improvements in maximal inspiratory and expiratory pressures are consistent with the concept that the observed weight gain is due to an increase in muscle mass. The small size of the obese group and the exclusion of patients with BMI greater than 31.1 kg/m^2 (males) or 32.3 kg/m^2 (females) also limit our ability to make firmer conclusions about obese patients with respect to their changes in BMI over time. The NETT protocol did not include measures of inflammatory cytokines or hormones, or nutritional evaluation such as anthropometric and metabolic parameters, to validate the results from prior studies. Last, events after randomization such as exacerbations, hospitalizations, and complications that could have had an effect on weight change were not accounted for in our analysis.

Nevertheless, our study imparts a significant contribution to our current understanding of the beneficial effects of LVRS. Our findings of weight gain after LVRS validate the findings in previous smaller studies in a large cohort of well-characterized patients in a randomized controlled trial and provide greater understanding of the patient profiles that gain weight after LVRS. We showed that weight gain is associated with changes in spirometry, respiratory muscle strength, lung volumes and ventilatory efficiency after LVRS. These physiological changes may be at least partially responsible for the weight gain in patients who undergo LVRS. In addition, a thorough and rigorous nutritional, hormonal, and metabolic assessment before LVRS may allow better prediction of changes in body composition and weight after surgery.

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